REMARKS

Claims 1, 3-8, 10-18, 20-26, and 28-48 were pending in the present application. Claims 49-64 have been added. Accordingly, claims 1, 3-8, 10-18, 20-26, and 28-64 are now pending. Support for new claims 49-64 can be found throughout the specification and in the claims as originally filed. No new matter has been added.

Phone interview

Applicant's attorney thanks the Examiner for the courtesy of the phone interview on October 22, 2003 regarding the Declaration which was filed with the response of January 21, 2003.

Drawings

In response to the draftsman's objections to the drawings, Applicant submitted a formal set of drawings with the Notice of Appeal which was mailed on October 24, 2003.

Rejection of 1, 3-8, 10-18, 20-26, and 28-48 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1, 3-8, 10-18, 20-26, and 28-48 under 35 U.S.C. §112, first paragraph. The Examiner states that while the specification is, "enabling for a method of treating a xenogeneic subject having spinal cord damage arising from amyotrophic lateral sclerosis or spinal cord injury," the specification, "does not reasonably provide enablement for treating a xenogeneic subject having spinal cord damage arising from the claim-designated neurodegenerative disorders or aging." This rejection is respectfully traversed.

The pending claims are directed to a composition for transplantation into a mammalian xenogeneic subject comprising isolated spinal cord cells obtained from an embryonic pig of between about 24 and about 35 days of gestation, such that treatment of spinal cord damage that would benefit from survival and integration of the spinal cord cells is obtained upon transplantation into the subject. The pending claims are also directed to a method of treating a mammalian xenogeneic subject having spinal cord damage that would benefit from survival and integration of porcine spinal cord cells by administering to the subject a composition comprising isolated spinal cord cells obtained from an embryonic pig of between about 24 and about 35 days of gestation, such that

treatment of spinal cord damage is obtained upon administration of the composition to the subject.

Applicant maintains for the following reasons and those of record that the instant specification fully enables one of ordinary skill in the art to treat spinal cord damage that would benefit from survival and integration of isolated spinal cord cells obtained from an embryonic pig. Applicant provides working examples in the specification of successful xenogenic transplantations using embryonic porcine spinal cord cells, using a mouse model for amytrophic lateral sclerosis (ALS) and another mouse model for spinal cord injury. The Examiner has indicated that the specification is enabling for spinal cord injury and ALS, which were included in the working examples of the specification. Applicant maintains, however, that examples describing animal models related to spinal cord injury and ALS were used to represent different types of spinal cord damage which would benefit from the instant invention ***and were not meant to limit the claimed invention.***

In Applicant's previous response mailed January 21, 2003, Applicant provided additional evidence that spinal cord damage, including damage resulting from neurodegenerative disorders and spinal cord injuries, can be treated using the claimed methods. Applicant submitted a Declaration which contained results obtained from Phase I clinical trials approved by the FDA which clearly demonstrated that the specification of the instant invention fully enables one of ordinary skill in the art to use the claimed compositions and methods for treatment of spinal cord damage in general, not just for treatment of ALS and spinal cord injury. The Declaration described transplantation of embryonic porcine spinal cord cells into human subjects having various types of spinal cord damage, including spinal cord injury resulting from trauma to both the upper (cervical) and lower (lumbar) regions of the spinal cord and transverse myelitis (TM), a neurodegenerative disorder. Data presented by Applicant demonstrated that

transplantation of porcine cells into damaged spinal cord can improve both the motor and sensory function of the subjects.

The Examiner has stated that the Declaration is not persuasive, "because the description of the transplantation procedure is incomplete and therefore it is impossible to know if the transplantations were carried out in accordance with the teachings of the specification." In response, Applicant provides herewith instructions (attached as Appendix A) which were provided for the physicians performing the xenogeneic transplantations described in the previously submitted Declaration.

The attached protocol shows that porcine spinal cord cells were administered directly to the spinal cord of the subject in the clinical trials. The physician was instructed to suspend the cells prior to administration, and then told to ***directly inject*** the cell suspension into the spinal cord of the subject. As shown in Appendix A, the instructions note that the number of injections warranted for the transplantation depends on the extent of the spinal cord damage.

The protocol detailed in Appendix A is well-supported by the teachings of the instant specification. Applicant teaches in the specification that porcine spinal cord cells can be introduced to a subject using the appropriate delivery method, stating that "a common method of administration of cells into the spinal cord of a subject is be ***direct stereotaxic injection*** of the cells into the area of spinal cord damage," (see page 13, lines 36-39 of the specification). In accordance with the teachings of the specification, successful transplantations were performed by ***directly injecting*** porcine cells into the damaged area of the spinal cord, as described in Appendix A. The instant specification teaches that porcine cells "can be inserted into a delivery device which facilitates introduction, e.g., injection, of the cells into the subjects....[t]he porcine cells of the invention can be inserted into such a delivery device, e.g., micropipette or syringe, in the form of a solution." (see page 14, lines 24-29 of the specification). As described in

Appendix A in accordance with the specification, the porcine cells were injected into the spinal cord of the subject using a needle/syringe.

Applicant teaches in the specification that the administration dosage of porcine cells can be determined by performing experiments in rats, as well as how to extrapolate the dosing of human equivalents from the rat experiments (see page 14, lines 3-13 of specification). In addition, Applicant provides an exemplary dosage in Example I, teaching that transplantations can be performed with an approximate concentration of cells at 100,000 cells per microliter (see page 27 of the specification). The instructions provided in Appendix A teach that "[t]he volume of cells to be injected at each site is a maximum of 20 microliters, which is equal to 2 million cells." Thus, as described as a working example of the instant specification, the concentration of the cell suspension in the instructions of Appendix A is 100,000 cells per microliter.

The protocol described in Appendix A is consistent with the teachings of the instant specification and was used to successfully treat patients with spinal cord damage who would benefit from survival and integration of embryonic pig spinal cord cells, as shown in the previously submitted Declaration. Thus, Applicant submits that the specification fully enables one of skill in the art to perform the claimed transplantation without undue experimentation, evidenced by the protocols which were used in actual clinical transplantations.

The Examiner has cited a number of references in support of the assertion that Applicant has not enabled the claimed invention because "[t]he art demonstrates that methods of xenotransplantation of neural tissue is unpredictable due to the immune response of the host." The Examiner cites Brevig *et al.* as teaching that immunosuppressive treatment is " 'inadequate at protecting neural xenografts' " and describes a case study of a transplantation recipient with Parkinson's disease who rejected his graft. Applicant submits that the issues discussed in Brevig reference are specific to xenotransplantations relating to the brain and are contradictory to the data presented by

Applicant in the specification as well as the clinical data presented in the previous Declaration. The working examples of the specification and the Declaration demonstrate that the claimed methods and compositions of porcine spinal cord cells for use in xenotransplantation produce predictable, successful results.

The Examiner cites Larsson *et al.* as providing a "detailed discussion of rejection mechanisms" particularly relating to complications which can arise from compromising the blood-brain barrier during the transplantation procedure. In contrast to the Examiner's assertion, the Larsson reference describes a ***successful*** xenogeneic transplantation in the brain, wherein the authors note in their conclusion that that longer survival would be likely with "more effective immunosuppressive drug treatments" other than cyclosporine which was used in the experiments. The authors cite the "immunoprivileged" environment of the brain as presenting unique challenges, and conclude that the immunosuppressive therapy which was chosen for the described experiments was "not sufficient." This observation does not undermine the overall success of the transplantations described in the Larsson reference, which demonstrate that transplantation of porcine neural tissue into a rat model for Parkinson's disease can improve behavioral defects.

The Examiner also cites Armstrong *et al.* as teaching that "graft rejection remains as a significant issue and that more effective immunosuppressive drug treatments are needed." The Armstrong reference describes experiments which examine the rejection of neural precursor cells which have been expanded in non-immunosuppressed rats. The authors conclude that expanding the porcine cell population with neural stem cell mitogens ***can reduce*** the immunogenicity of the transplanted cells. Thus, the Armstrong reference provides additional methods for reducing immunogenicity of cells used in a xenogeneic transplantation. Applicant submits that the Armstrong reference does not support the notion that xenotransplantation is unpredictable, but rather provides additional measures which can be taken to promote tissue acceptance in the recipient.

Furthermore, the Brevig, Armstrong, and Larsson references cited by the Examiner relate specifically to xenotransplantation of ***brain tissue.*** The Armstrong reference describes transplantation of fetal neural precursor cells obtained from the cerebral cortex of fetal pigs, while the Larsson reference describes transplantation of fetal ventral mesencephalon cells. Applicant submits that these references pertaining to xenotransplantation of ***brain tissue*** do not demonstrate the asserted unpredictability of claims pertaining to xenotransplantation of ***spinal cord*** cells.

The Examiner has also cited Rowe and Dorling *et al.* as providing "additional discussion of the challenges of xenotransplantation." Both of these cited references relate to ***whole organ*** transplantation, in contrast to the claimed invention which specifies a composition comprising ***isolated spinal cord cells***. The Examiner states that the Dorling reference teaches hyperacute rejection (HAR) as a challenge to xenotransplantation. Applicant points out that the Dorling reference teaches HAR in the context of whole organ transplants, specifying that "different organs whose differing degrees of susceptibility to HAR, with livers and lungs being relatively resistant" (see page 868, column 1). The instant specification, as well as the results provided in the Declaration, provides evidence that efforts can be taken, *e.g.*, immunosuppressive drugs and/or masking of cells, to reduce the risk of rejection of the xenotransplanted cells. Moreover, certain of the pending claims are directed to embodiments of the invention in which cells or subjects are treated to minimize the risk of rejection.

Applicant maintains that as evidenced by the successful Phase I clinical transplantations described in the previously submitted Declaration and the successful examples of xenogeneic transplantation described in the specification, one of ordinary skill in the art would be able to make and use the claimed compositions and practice the claimed methods given the teachings of the instant specification and using no more than routine experimentation.

With respect to treatment of specific disease states, in the Office Action mailed April 24, 2003, the Examiner acknowledged that the specification is enabling for spinal cord injury and ALS. Applicant respectfully requests that the Examiner indicate that

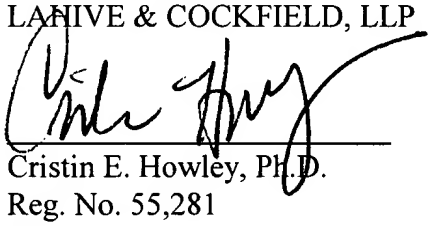
previously pending claims 36, 38, and 48, and new claims 49-64 be indicated allowable, as these claims relate specifically to spinal cord injury and ALS.

Moreover, with respect to other conditions, Applicant points out that the Phase I clinical trials approved by the FDA were conducted on a variety of patients suffering from spinal cord injury resulting from trauma to both the upper (cervical) and lower (lumbar) regions of the spinal cord and a neurodegenerative disorder, transverse myelitis (TM). Applicant maintains that the specification provides ample support for use of porcine spinal cord cells for treatment of spinal cord damage as claimed, resulting from, *e.g.*, neurodegenerative disorders. Applicant respectfully submits that the teachings in the specification enable the treatment of a variety of different types of deficits that would benefit from transplantation of fetal spinal cord cells.

CONCLUSION

It is respectfully submitted that this application is in condition for allowance. If the Examiner believes that a telephone conversation with Applicant's Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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APPENDIX A

Title: Administration of Porcine Spinal Cord Cells (SCIR)
Document Number: BR0055-0

Revision: 00
Effective Date APR 12 2001

Patient Number: WDS-03 Date: 6/12/01

Received on: 6/12/01

Product Lot Number: SciC007 Time of Arrival of Cells: 8:00 AM

1. The site of damage within the spinal cord will be localized by MRI. A laminectomy will be performed at a location one segment above or below the site of damage. With the spinal cord revealed, the dura will be opened and a needle inserted into the spinal cord to deliver the cells.

NOTE: **All draws of fluid must be done very slowly to prevent bubble formation.**

2. Gently resuspend (do not shake) the cells for transplant (which have collected into a pellet) by repetitively rotating the vial 90° to the right and to the left until the pellet of cells has dislodged and a uniformly cloudy suspension is achieved.

3. Place the tip of the needle in the cryovial containing the cell suspension for transplant and draw up a maximum of 20 µl.

4. Cells will be delivered to the selected site of the spinal cord bilaterally, and along the entire segment. The distance between tracts along the segment will be approximately 1 – 3 mm. Effort should be made to evenly space the bilateral distance between injection tracts. The exact number of injections will be dependent on the segment of the cord being transplanted because of the variation in the size of segments along the spinal cord.

5. The cells must be injected slowly into the spinal cord to avoid cells being forced back along the needle tract and out of the target site. The volume of cells to be injected at each site is a maximum of 20 microliters, which is equal to 2 million cells. Once the target site is selected, the needle is inserted approximately 3 – 7 mm deep into the spinal cord targeting the ventral horn gray matter. Cells are to be injected at a rate of approximately 4 µl per minute until 10—20 µl cells are injected.

6. After the final injection of cells at a target site, the needle/syringe will be held in place for 2-5 minutes. This wait period will allow the cells and injection solution to equilibrate with surrounding tissue to minimize the chance of leakage of cells along the needle tract.

7. Remove the needle / syringe from spinal cord.

8. Record the following information on the attached form:

   - Injection site number
   - Start time (cannula inserted)
   - Stop time (removal of cannula)
   - Distance between deposits
   - Number of deposits

9. Repeat steps for each of the remaining injection tracts.